PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Iris PECKER et al. Group Art Unit: 1652

Application No.: 09/776,874 Examiner: R. Hutson

Filed: February 6, 2001 Docket No.: 120736

For: POLYNUCLEOTIDE ENCODING A POLYPEPTIDE HAVING HEPARANASE ACTIVITY AND EXPRESSION OF SAME IN GENETICALLY MODIFIED CELLS

DECLARATION UNDER 37 C.F.R. §1.132

I, Iris Pecker, a citizen of Israel, hereby declare and state:

1. I am a co-inventor of the above-identified patent application.

2. I have a Ph.D. in Molecular Biology, which was conferred upon me by Hebrew University of Jerusalem in Israel in 1994, after which I worked as a post-doctoral fellow at Tel Aviv University in Israel in the field of human genetics.

3. I have been employed by Insight Strategy & Marketing Ltd., now named InSight Biopharmaceuticals Ltd., since 1996 and am presently the head of the molecular biology department. I have over 10 years of work and research experience in molecular biology.

4. The above-identified patent application describes heparanase protein having heparanase catalytic activity or being cleavable so as to acquire heparanase catalytic activity. In particular, the application describes a heparanase protein having SEQ ID NO: 10. However, it is respectfully submitted that, based on the specification of the above-identified patent application, one of ordinary skill in the art would have been able, at the time of the present invention, to make and use heparanase proteins having sequences that are not identical to SEQ ID NO: 10. In particular, one of ordinary skill in the art would have been

able to modify the polypeptide of SEQ ID NO: 10 in order to form other proteins having heparanase catalytic activity or being cleavable so as to acquire heparanase catalytic activity. Specifically, one of ordinary skill in the art would have been able, by routine experimentation, to synthesize proteins having, for example, at least 70% homology with SEQ ID NO: 10 or a portion thereof, and to test these proteins (optionally after they have been cleaved) for heparanase catalytic activity.

5. In addition, the sequence comparisons between human, mouse and rat heparanase presented in Figure 17 of the above-identified patent application provide significant guidance as to modifications that can be made to the protein while retaining its heparanase catalytic activity.

6. Furthermore, one of ordinary skill in the art is well aware of the characteristics of the various amino acids and the types of amino acid substitutions that are more likely to maintain a functional protein.

7. Given the high level of skill in the art, it is respectfully submitted that the experimentation necessary to make and use heparanase proteins having sequences that are not identical to SEQ ID NO: 10, specifically heparanase proteins that have at least 70% homology with SEQ ID NO: 10 or a portion thereof, would not have been undue. In contrast, this type of experimentation would have been considered routine in the art.

8. U.S. Patent No. 5,362,641 to Fuks et al. (hereinafter "Fuks") purports to describe substantially purified heparanase obtained from the human SK-HEP-1 cell line. See the Abstract. However, the experiment described in Fuks did not actually result in substantially purified heparanase. Instead, the composition obtained by Fuks (hereinafter "the Fuks composition") contained a mixture of proteins. Proteins included in this mixture are listed in Appendix A attached hereto.

9. We identified proteins in the Fuks composition by micro-sequencing. There are detection limitations to micro-sequencing. Thus, the fact that proteins other than heparanase were identified by micro-sequencing indicates that a substantial amount of these proteins were present in the Fuks composition.

10. Fuks also purports to describe the formation of antibodies directed against heparanase. Col. 10. However, subsequent research has revealed that these antibodies were actually anti-PAI-1 antibodies, PAI-1 being a significant protein that was present in the Fuks composition.

11. As described in U.S. Patent No. 6,177,545, of which I am a co-inventor, once truly isolated heparanase was obtained, we were able to obtain anti-heparanase antibodies. Thus, the fact that anti-PAI-1 antibodies and no detectable level of anti-heparanase antibodies were raised by the Fuks composition clearly indicates that the Fuks composition contained a major amount of PAI-1 relative to the amount of heparanase.

12. Based on the presence of significant amounts of proteins other than heparanase, specifically PAI-1, one of ordinary skill in the art would not refer to the Fuks composition as "isolated heparanase protein." Similarly, one of ordinary skill in the art would not refer to the Fuks composition as heparanase protein "purified close to homogeneity."

13. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: 12/10/04 Iris Pecker

Dr. Iris Pecker

Appendix A

The proteins identified by the inventors following the performance of Mono-S HPLC purification were found to be as follows: PAI-1, Nexin-I, Vimentin, Grp94/endoplasmin, FLT receptor, Tryptase.